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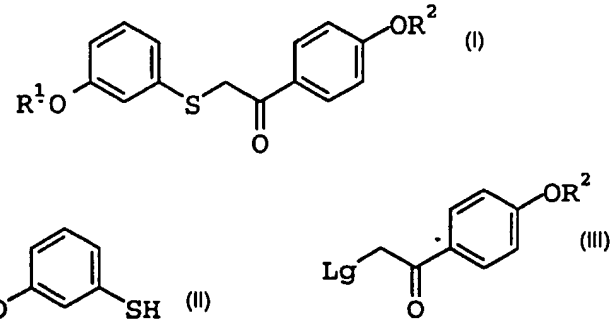
[Continued on next page]

(54) Title: PROCESS FOR PREPARING $G(A)-(3-ARYLTHIO)-ACETOPHENONES



(57) Abstract: The present invention relates to a biphasic process for preparing a compound of formula (I) from a compound a compound of formula (II) and (III).

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MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)

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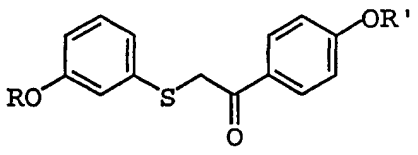
PROCESS FOR PREPARING α-(3-ARYLTHIO)-ACETOPHENONES

BACKGROUND OF THE INVENTION

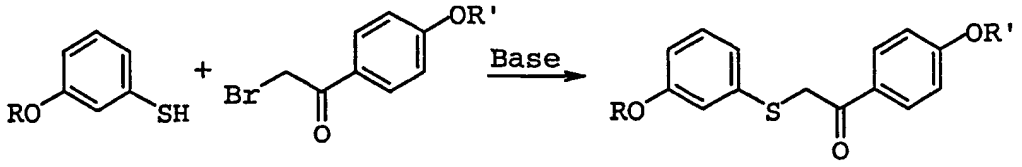
Compounds of the formula:



;

wherein R and R' are the same or different hydroxy protecting group; are intermediates to pharmaceutically active compounds (see, *e.g.*, U.S. Patent No.'s 4,075,227, 4,133,814, 4,418,068, 5,552,401 and 5,723,474).

According to the procedures described in the above mentioned patents, these intermediates are constructed via the following coupling reaction:

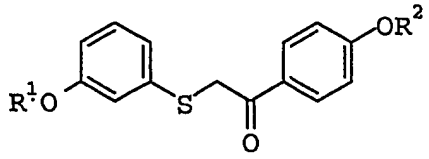


wherein the reaction is performed neat in, *e.g.*, pyridine or is performed in the presence of aqueous ethanolic potassium hydroxide. In either case, said reactions are performed in a homogenous aqueous miscible environment.

When produced by this procedure, purification of the compound of formula I would typically involve the addition of an organic solvent (aqueous immiscible) to facilitate separation of the product (which is soluble in the organic layer) from the inorganic aqueous soluble impurities. The aqueous layer would typically be removed followed by one or more aqueous acidic and basic extractions of the organic layer to remove residual base and inorganic salts.

BRIEF SUMMARY OF THE INVENTION

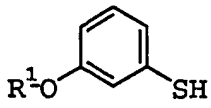
The present invention relates to a process for preparing a compound of formula I:



I;

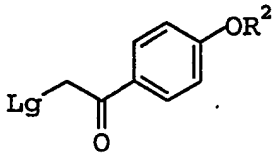
wherein:

R^1 and R^2 are independently selected from the group consisting of hydrogen and a hydroxy protecting group; which includes reacting a compound of formula II:



II;

dissolved in a suitable alkaline aqueous solvent; with a compound of formula III:



III

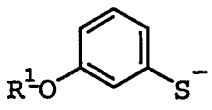
wherein Lg is a leaving group; dissolved in a suitable aqueous immiscible solvent.

DETAILED DESCRIPTION OF THE INVENTION

General terms used in the description of chemical formulas bear their usual meanings. For example, the term "hydroxy protecting group" denotes a group understood by one skilled in the organic chemical arts of the type described in Chapter 2 of "Protective Groups in Organic Synthesis, 2nd Edition, T. H. Greene, *et al.*, John Wiley & Sons, New York, 1991, hereafter "Greene".

Representative hydroxy protecting groups include, for example, C_1-C_6 alkyl and substituted C_1-C_6 alkyl, including methyl, ethyl, isopropyl, cyclopropyl, methoxymethyl, methylthiomethyl, *tert*-buylthiomethyl, (phenyldimethylsilyl)methoxymethyl, benzyloxymethyl, *p*-methoxy-benzyloxymethyl, *tert*-butoxy-methyl; ethoxyethyl, 1-(2-chloroethoxy)ethyl, 2,2,2-trichloroethoxymethyl, and 2-(trimethylsilyl)ethyl; phenyl and substituted phenyl groups such as *p*-chlorophenyl, *p*-methoxyphenyl, and 2,4-dinitrophenyl; benzyl groups; alkylsilyl groups such as trimethyl- triethyl- and triisopropylsilyl; mixed alkylsilyl groups such as dimethylisopropylsilyl, and diethylisopropylsilyl; acyl protecting groups such as those of the general formula COC_1-C_6 alkyl or COAr; and esters of the general formula CO_2C_1-C_6 alkyl, or CO_2Ar, where Ar is phenyl or substituted phenyl as described above.

The term "leaving group" refers to an atom, or group of atoms that in the aggregate are susceptible to nucleophilic displacement by a thiolate anion, more specifically, to the thiolate shown below:



Examples of such leaving groups include halides such as Cl, Br and I; sulfonates (a group of the general formula OSO_2R^3 where R^3 is optionally substituted C_1-C_6 alkyl or optionally substituted phenyl) such as methanesulfonate or toluenesulfonate; and phosphonates (a group of the general formula OPO_2R^3) such as methyl phosphate, ethyl phosphate or phenyl phosphate.

The term "suitable alkaline aqueous solvent" refers to a suitable base dissolved in water wherein the resulting mixture sufficiently solubilizes the compound of formula II to afford a medium within which to effect the desired

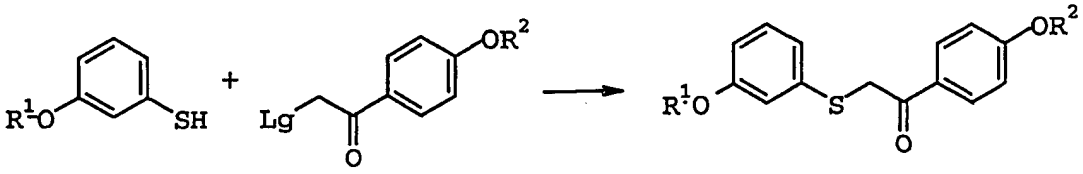
deprotonation, i.e., the desired thiolate formation.

The term "suitable base" refers to a base that is soluble in water and is sufficiently basic to deprotonate the thiol of formula II. Examples of bases that can accomplish this deprotonation are carbonates, bicarbonates, phosphates and hydroxides, for example, lithium, cesium, sodium, potassium or magnesium carbonate, bicarbonate, or hydrogen phosphate, phosphate or hydroxide.

The term "aqueous immiscible solvent" refers to a solvent or mixture of solvents wherein the resulting mixture is substantially immiscible with water and sufficiently solubilizes the compound of formula III to afford a medium that, at the interface of the aqueous and aqueous immiscible phases, is capable of effecting the desired coupling reaction. Such aqueous immiscible solvents are readily apparent to the skilled artisan and include methylene chloride, chloroform, 1,2-dichloroethane, ethyl acetate, isopropyl acetate, amyl acetate, toluene, chlorobenzene, methyl t-butyl ether, mixtures thereof, and the like.

The biphasic process of the present invention is illustrated in Scheme 1 below.

Scheme 1



II in aqueous alkaline phase

III in aqueous immiscible phase

I in aqueous immiscible phase

The present process includes deprotonating the thiol of formula II in an aqueous medium to make an aqueous solution of the thiolate. The deprotonation may be conducted by adding the thiol, to aqueous base or adding base to an

aqueous mixture of the thiol. Initial preparation of the aqueous base is preferable to facilitate dissolution of the base and to control the heat of dissolution when bases like sodium or potassium hydroxide are used. Use of hydroxide bases such as sodium or potassium hydroxide are preferable as the formation of the thiolate with these bases do not result in the generation of gas.

The deprotonation is readily effected at ambient temperature. The thiols exhibit relatively low water solubility while the thiolate ions exhibit relatively high water solubility. Thus, the deprotonation reaction is preferably stirred until the solution is homogeneous. Preferably the concentration of the aqueous thiolate solution ranges from 0.8 to 1.5 molar.

A solution of the acetophenone III may be prepared by dissolving the acetophenone in a water immiscible solvent, preferably ethyl acetate. Preferred leaving groups include chloride and bromide as the corresponding compounds of formula III are readily prepared by ω-chloronation or bromination of the corresponding acetophenone. ω-Chloroacetophenones is most preferred. Preferably the solution concentration ranges from 0.5 to 1 molar. The thiolate and organic solution of III are combined and stirred between 15 and 50°C. While complete reaction is typically achieved in 1 to 3 hours at ambient temperature elevated temperatures may be used to increase solubility of the acetophenone derivative and the reaction product. After the reaction is complete the phases are separated and the desired product can be crystallized from the organic phase by either concentration or addition of an anti-solvent or a combination of both. The most preferable anti-solvents are heptanes or hexanes.

The time required to effect the overall transformation will be dependent upon the temperature at which the

reactions are run. Therefore, the progress of the reactions should be monitored via conventional techniques, *e.g.*, HPLC, to determine when the reactions are substantially complete. Monitoring the progress of chemical reactions is well within the ordinarily skilled artisan's capability.

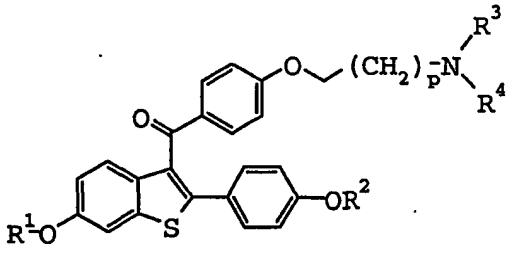
Preferred compounds of formula II for use in the present process are those where R^1 is hydrogen, methyl, isopropyl or benzyl, particularly hydrogen, methyl or benzyl. Preferred compounds of formula III for use in the present process are those where R^2 is hydrogen, methyl, isopropyl or benzyl, particularly methyl. Thus, preferred products of the above reaction include, but are not limited to, α-(3-hydroxyphenylthio)-4-methoxyacetophenone, α-(3-methoxyphenylthio)-4-methoxyacetophenone, α-(3-isopropoxyphenylthio)-4-methoxyacetophenone, and α-(3-benzyloxyphenylthio)-4-methoxyacetophenone.

As stated above, the process of the present invention is performed in a biphasic reaction medium. In general, biphasic reactions are expected to proceed at a diminished rate, relative to the corresponding mono-phasic reaction. However, biphasic reactions can offer an advantage with product purification. That is, purification is sometimes much simpler and efficient with a biphasic reaction when the product is mostly soluble in one phase and the impurities are mostly soluble in the other. To overcome reaction rate liabilities, phase transfer catalysts are typically employed in biphasic systems. Surprisingly, the present process proceeds at rates and in yields comparable to the prior art mono-phasic rates even in the absence of a phase transfer catalyst.

Furthermore, when R^1 is hydrogen in the compound of formula II, *i.e.*, when the compound of formula II is unprotected, Applicants have found that the present process proceeds without significant undesired "O-alkylation". This

surprising characteristic of the present process enables the direct synthesis of a compound of formula I where one of R^1 or R^2 is hydrogen.

In a preferred embodiment, a compound of formula I is cyclized, acylated, optionally deprotected and optionally salified to form a compound of formula IV:



IV

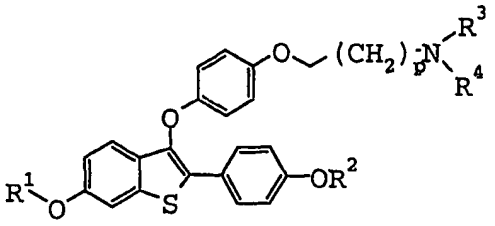
or a pharmaceutical salt thereof; wherein:

p is 0, 1 or 2; and

R^3 and R^4 are independently C_1-C_4 alkyl, or combine together with the nitrogen to which they are attached to form a piperidinyl, pyrrolidinyl, methylpyrrolidinyl, dimethylpyrrolidinyl, morpholino, dimethylamino, diethylamino, or 1-hexamethyleneimino ring.

The cyclization, acylation and optional deprotection and salification reactions may be performed essentially as described in U.S. Patent No.'s 4,380,635, 4,418,068, 5,512,684, 5,523,416, 5,629,425, 5,731,327, 5,969,157 and 5,977,383 the teachings of each are herein incorporated by reference. The hydrochloride salt of a compound of formula IV where R^1 and R^2 is hydrogen and R^3 and R^4 combine to form a piperidinyl ring is a preferred product.

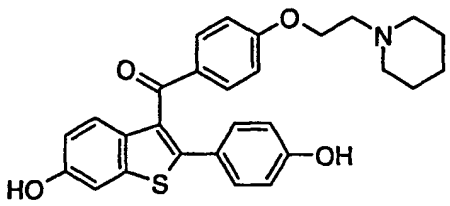
In another preferred embodiment, a compound of formula I may be cyclized, 3-halogenated, S-oxidized, have the 3-halo group displaced, reduced, optionally deprotected, and optionally salified to prepare a compound of formula V:



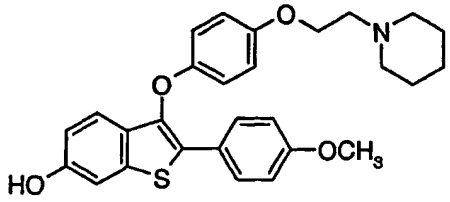
V;

or pharmaceutical salt thereof.

In a particularly preferred embodiment, a compound of formula I may be used to prepare a compound of formula VII and VIII:



VII



VIII.

The cyclization, 3-halogenation, oxidation, nucleophilic displacement of halo, reduction, and optional deprotection and salification reactions may be performed essentially as described in U.S. Serial No. 09/XXX,XXX (Attorney Docket No. X-14146) filed on the same day as X-14145; U.S. Patent No.'s 5,510,357, 5,512,684, 5,523,416, 5,723,474, 5,969,157 and 5,977,383; and PCT Publication No.'s WO 01/09115 and WO 01/09116, the teachings of each are herein incorporated by reference. The hydrochloride salt of compound of formula V where R^1 is hydrogen, R^2 is methyl, and R^3 and R^4 combine to form piperidinyl is preferred.

Compounds of formula II and III are known in the art and are generally commercially available or can be prepared by methods well known in the art from readily available starting materials.

Examples

Preparation 1

Preparation of α-bromo-4-hydroxyacetophenone

To a rapidly agitated solution of 65.0 gm of 4-hydroxyacetophenone in 880 mls of ethyl acetate was added 23 ml of bromine over a 1 hour period. After the addition was complete the reaction mixture was heated to 60°C and stirred for 45 min. during which time it developed a deep purple color. The hot solution was quenched with 400 ml of water and the phases separated. The organic phase was washed with aqueous sodium bisulfite (2.14 gm dissolved in 150 ml of water). The ethyl acetate solution of α-bromo-4-hydroxyacetophenone was used as is.

Example 1

Preparation of α-(3-methoxyphenylthio)-4-methoxyacetophenone

An aqueous solution of potassium hydroxide is prepared by dissolving 4.46 gm of potassium hydroxide flakes in 36.8 ml of water. In a separate vessel, 8.59 gm of α-chloro-4-methoxyacetophenone and 50 ml of ethyl acetate are combined and warmed to 35°C to effect dissolution. At ambient temperature, 7.01 gm of 3-methoxybenzenethiol are added to the aqueous solution of base. Immediately after addition of the thiol, the warm ethyl acetate solution of the α-chloride

is added. The resulting bi-phasic reaction mixture is stirred at 30°C for 3 hours. The phases are separated. The desired product is crystallized by dropwise addition of 200 mls of hexane at 20-25°C. The resulting crystalline slurry is cooled to -10°C and stirred for 2 hours. The solids are isolated by filtration, washed with hexane, and dried at 30°C under vacuum overnight to afford 12.44 gm of product. ^{1}H and ^{13}C NMR spectra were consistent with that of the desired product.

Example 2

Preparation of α-(3-hydroxyphenylthio)-4-methoxyacetophenone

An aqueous solution of potassium hydroxide is prepared by dissolving 6.28 gm of potassium hydroxide pellets in 50 ml of water. The solution was adjusted to ambient temperature and 10.0 gm of 3-hydroxybenzenethiol was added with a 16.5 ml water rinse. The reaction mixture was stirred for approximately 10 minutes until homogeneous and a solution of 14.64 gm of α-chloro-4-methoxyacetophenone dissolved in 120 ml of ethyl acetate was added with a 14 ml ethyl acetate rinse. The ethyl acetate solution of ω-chloro-4-methoxyacetophenone was warmed slightly to effect complete dissolution of the ω-chloride prior to the addition. The bi-phasic reaction mixture was stirred for 3 hours at ambient temperature. The phases were separated and the organic phase concentrated to a total volume of 67 ml by reduced pressure rotary evaporation. At ambient temperature 260 ml of heptanes was added dropwise over a 45 minute period to effect precipitation of the product. The resulting crystalline slurry was stirred for 1 hour at ambient temperature, filtered, washed with 50 ml of heptanes and the isolated solids vacuum dried overnight at 60°C. The

dried white solid from two identical runs weighted 20.34 gm and 20.27 gm respectively. ^{1}H and ^{13}C NMR spectra were consistent with that of the desired product.

Example 3

Preparation of α-(3-methoxyphenylthio)-4-hydroxyacetophenone

The following reaction was conducted under a nitrogen atmosphere. To a solution of 37.82 gm of potassium hydroxide in 350 ml of water was added 66.9 gm of 3-methoxybenzenethiol with a 25 ml water rinse. The reaction mixture was stirred for approximately 10 minutes to effect deprotonation of the thiol and formation of a homogeneous solution of the thiolate. The ethyl acetate solution of α-bromo-4-hydroxyacetophenone from Preparation 1 was added. The addition was accompanied by a slight exotherm to 43°C. After stirring the biphasic solution for 1 hour, HPLC assay showed the reaction was complete. The phases were separated and the organic phase washed with 200 ml of dilute aqueous sodium bicarbonate. The organic phase was dried over sodium sulfate and stripped of solvent to afford a light orange-tan solid. The crude solid was recrystallized from 100 ml of hot methanol to afford 82.12 gm of a light purple crystalline solid. ^{1}H and ^{13}C NMR spectra were consistent with that of the desired product.

Example 4

Preparation of α-(3-hydroxyphenylthio)-4-hydroxyacetophenone

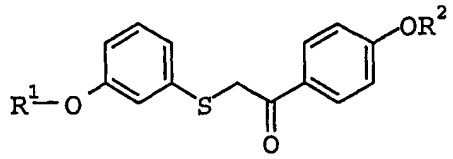
To a solution of 31.51 gm of potassium hydroxide in 300 ml of water was added 60.24 gm of 3-hydroxybenzenethiol with a 25 ml water rinse. The reaction mixture was stirred for approximately 10 minutes until it consisted of a single

homogeneous phase. The ethyl acetate solution of α-bromo-4-hydroxyacetophenone from Preparation 1 was added with a 25 ml water rinse. The addition was accompanied by a slight exotherm to 40°C. After stirring the biphasic solution for 2 hours HPLC assay showed the reaction was complete. The phases were separated. The organic phase was concentrated by removal of 480 ml of distillate by atmospheric distillation. The resulting yellow solution was cooled to 60°C and 400 ml of heptanes were slowly added in a dropwise manner during which time the reaction temperature was allowed to cool to 50°C. This resulted in crystallization of the desired product. The crystalline slurry was allowed to cool to ambient temperature and an additional 400 ml of heptanes was added dropwise over a 1 hour period. The crystalline slurry was stirred for 1 hour. The solids were isolated by filtration, washed with 100 ml of heptanes and dried overnight at ambient temperature with a light nitrogen purge to afford 96.21 gm of product. ^{1}H and ^{13}C NMR spectra were consistent with that of the desired product.

CLAIMS

WE CLAIM:

1. A process for preparing a compound of formula I:

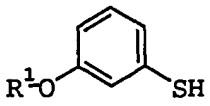


I;

wherein:

R^1 and R^2 are independently selected from the group consisting of hydrogen and a hydroxy protecting group;

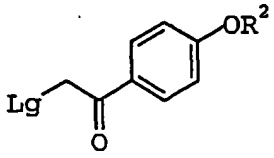
which comprises reacting a compound of formula II:



II;

dissolved in a suitable alkaline aqueous solvent;

with a compound of formula III:



III

wherein Lg is a leaving group;

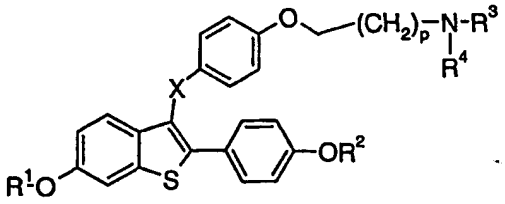
dissolved in a suitable aqueous immiscible solvent.

2. The process of Claim 1 wherein the compound of formula II is a compound where R^1 is H, benzyl, methyl or isopropyl and the compound of formula III is a compound where R^2 is H, benzyl, methyl or isopropyl.

3. The process of either Claim 1 or Claim 2 wherein the compound of formula II is a compound where R^1 is methyl or benzyl and wherein the compound of formula III is a compound where R^2 is methyl.

4. The process of any one of Claims 1-3 wherein the aqueous immiscible solvent is ethyl acetate.

5. In a process for preparing a compound of formula VI:



VI;

or an acid addition salt thereof;

wherein:

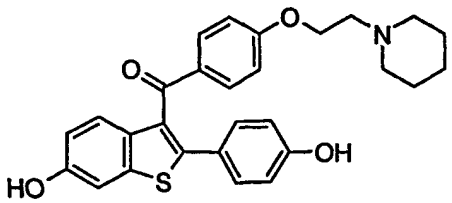
p is 0, 1 or 2;

R^3 and R^4 are independently C_1-C_4 alkyl, or combine together with the nitrogen to which they are attached to form a piperidinyl, pyrrolidinyl, methylpyrrolidinyl, dimethylpyrrolidinyl, morpholino, dimethylamino, diethylamino, or 1-hexamethyleneimino ring; and

X is O or CO;

the improvement which comprises the process of Claim 1.

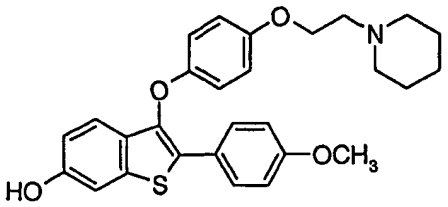
6. The process of claim 5 wherein the compound of formula VI is of the formula VII:



VII

or a pharmaceutically acceptable salt thereof.

7. The process of claim 5 wherein the compound of formula VI is of the formula VIII:



VIII

or a pharmaceutically acceptable salt thereof.